Tickborne Diseases: A Springtime Review of Diagnosis, Treatment and Prevention

Clinician Outreach and Communication Activity (COCA) Conference Call

April 10, 2014

Office of Public Health Preparedness and Response
Division of Emergency Operations

Objectives

At the conclusion of this session, the participant will be able to accomplish the following:

- **Discuss the geographic distribution of Lyme disease, Southern tick-associated rash illness (STARI), Rocky Mountain spotted fever, ehrlichiosis, and anaplasmosis.**
- **Explain the signs and symptoms of tickborne diseases.**
- **Describe the appropriate use of serologic tests for confirming diagnoses of tickborne diseases.**
- **State the appropriate use of antibiotics in treatment of tickborne diseases.**

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TODAY'S PRESENTER

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TODAY'S PRESENTER

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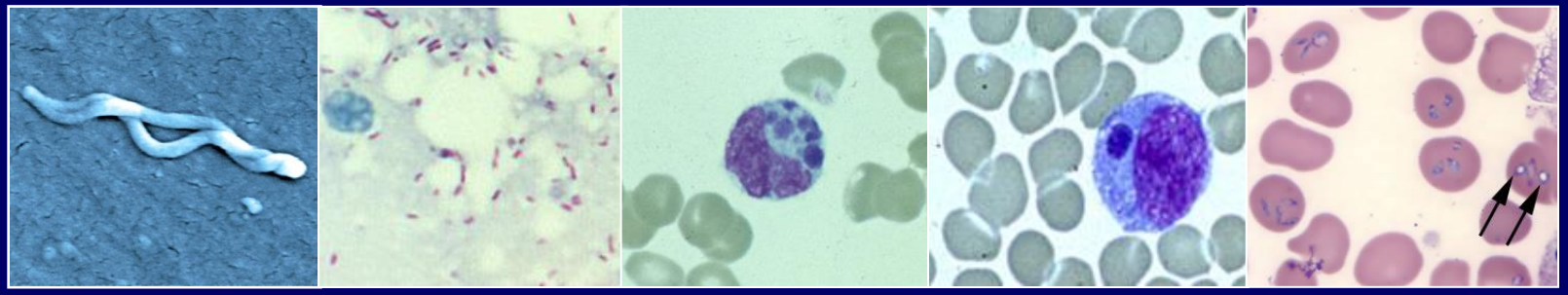
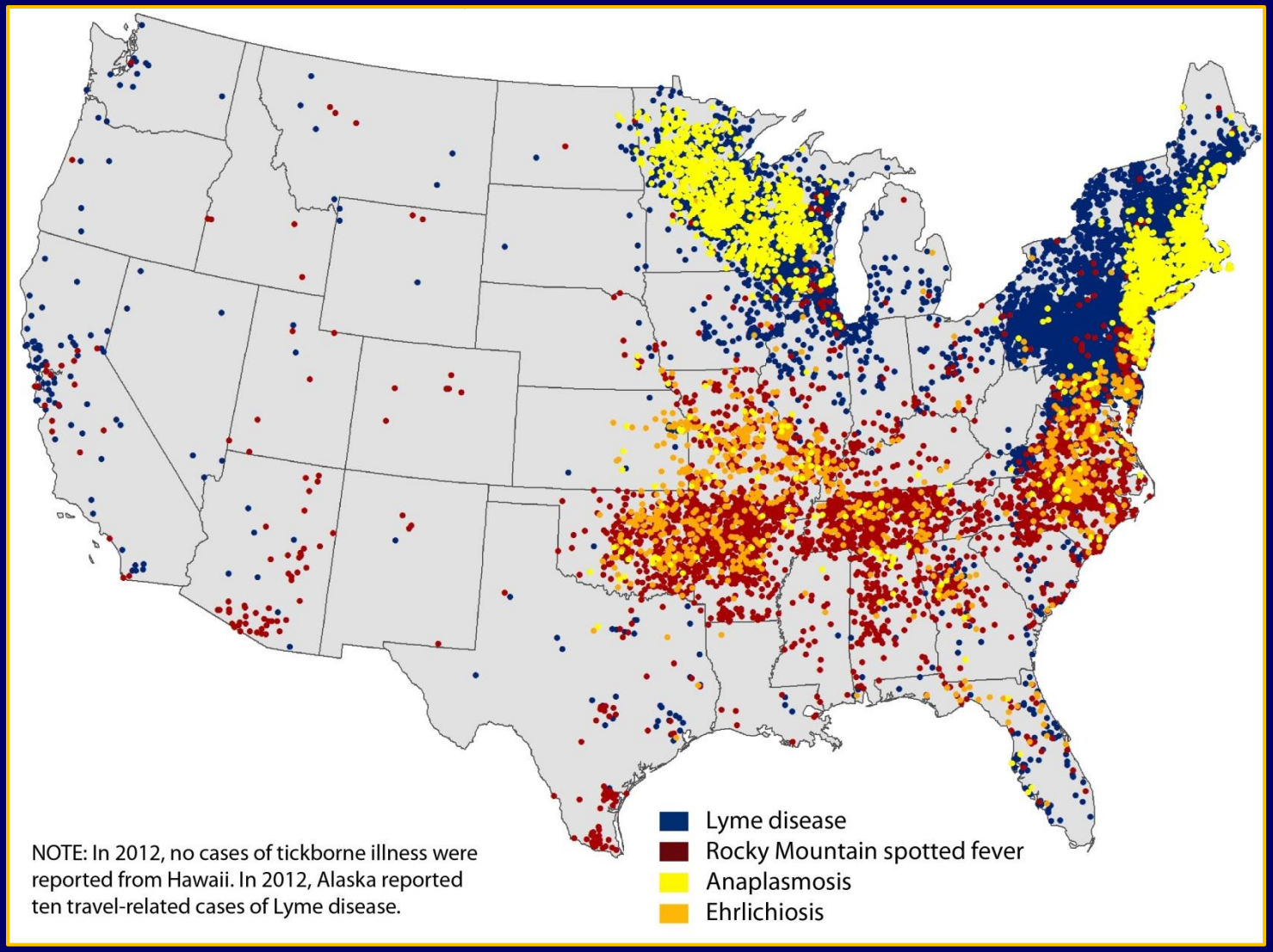
Leading Tickborne Diseases in US

- Lyme disease (*Borrelia burgdorferi*)
- Rocky Mountain spotted fever (*Rickettsia rickettsii*)
- Ehrlichiosis (*Ehrlichia chaffeensis*, others)
- Anaplasmosis (*Anaplasma phagocytophilum*)
- Babesiosis (*Babesia microti*)



For information on other tickborne diseases, visit www.cdc.gov/ticks

Distribution of Key Tickborne Diseases, 2012



Diseases reported to CDC by state health departments. Each dot represents one case. The county where the disease was diagnosed is not necessarily the county where the disease was acquired.

Number of Selected Tickborne Disease Cases Reported to CDC, 2012

Lyme disease[1]	30,831
Spotted Fever Rickettsiosis[1,2]	4,470
Anaplasmosis	2,389
Ehrlichiosis[3]	1,128

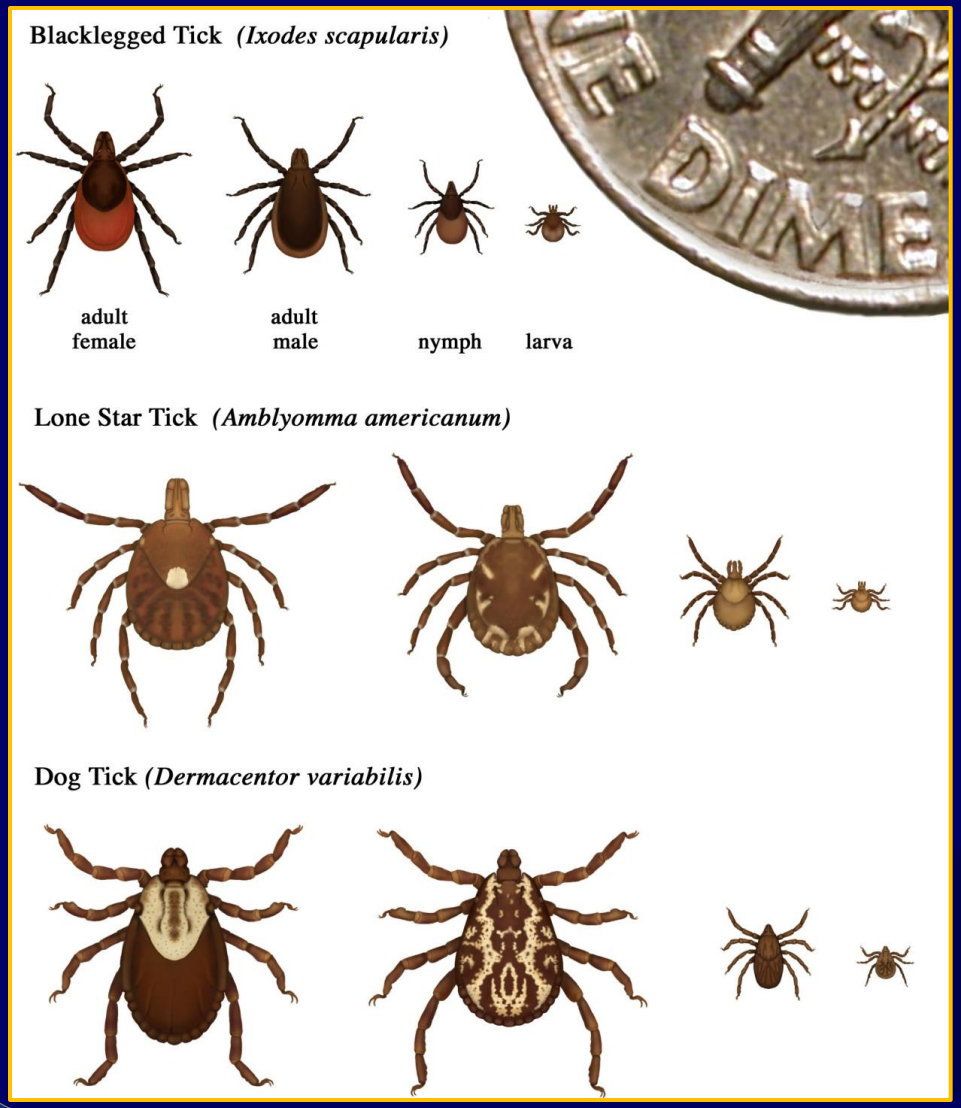
Source: Notifiable Diseases and Mortality Tables, August 23, 2013 / 62(33);669-682

[1] Confirmed and probable cases

[2] Includes Rocky Mountain spotted fever

[3] *Ehrlichia chaffeensis*

Selected Tick Vectors



Primary diseases transmitted:

→ Lyme disease
Anaplasmosis
Babesiosis
Powassan disease

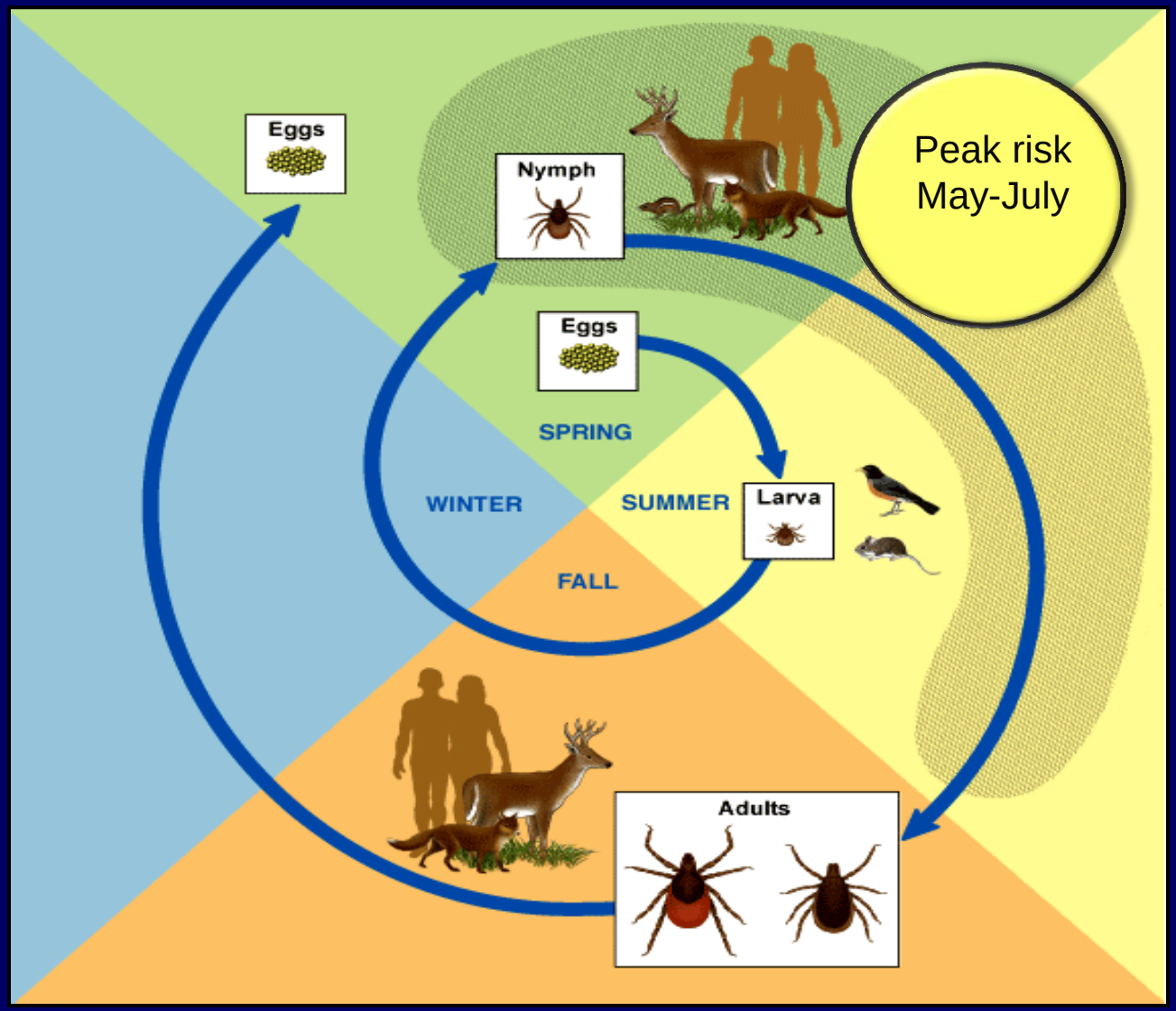
→ Ehrlichiosis
STARI
Tularemia

→ Rocky Mtn Spotted Fever
Tularemia

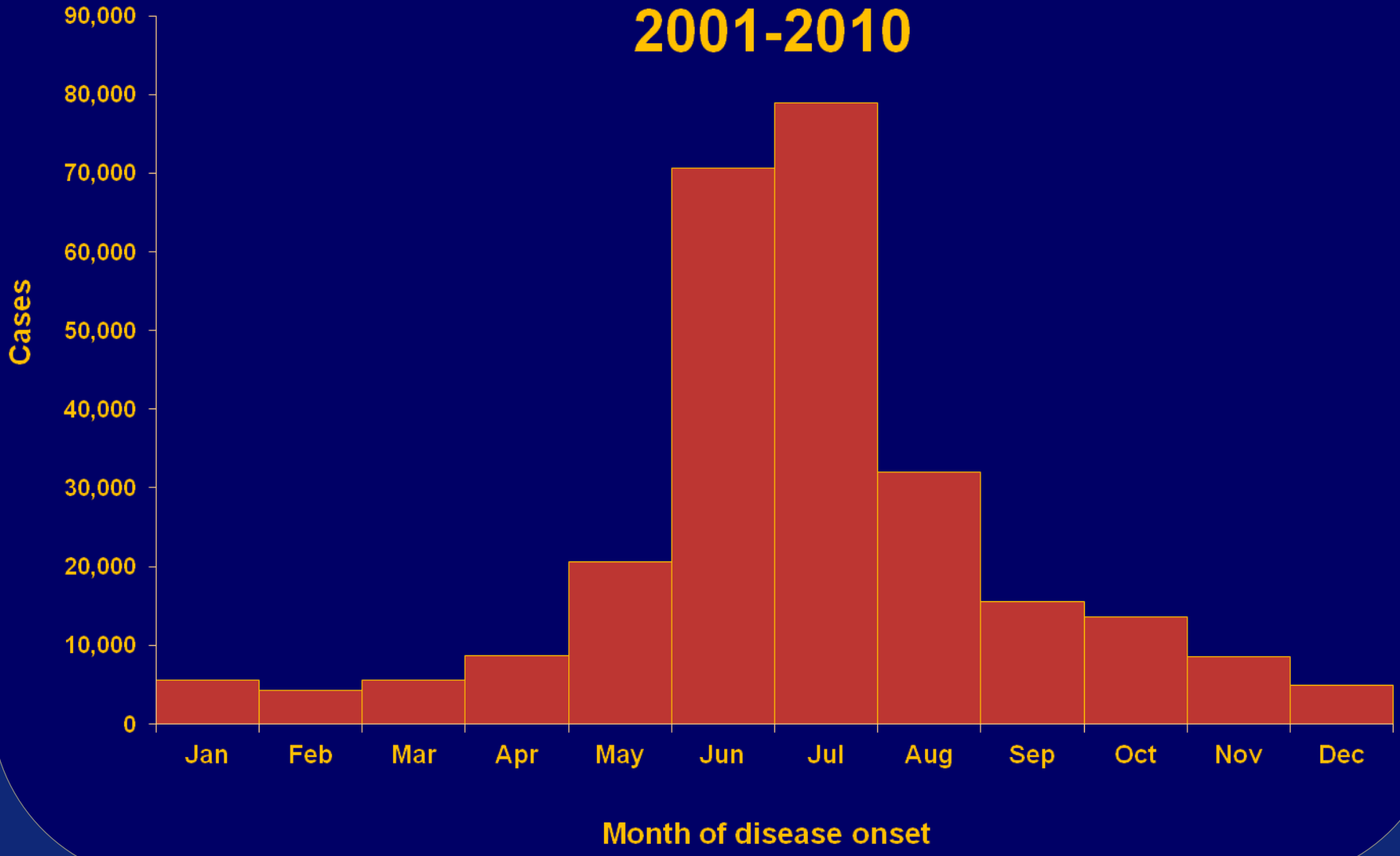
Lyme disease

- Caused by spirochete *Borrelia burgdorferi*
- Occurs in areas of North America, Europe, and Asia
- ~30,000 cases reported annually in US
- Transmitted in US by *Ixodes* ticks

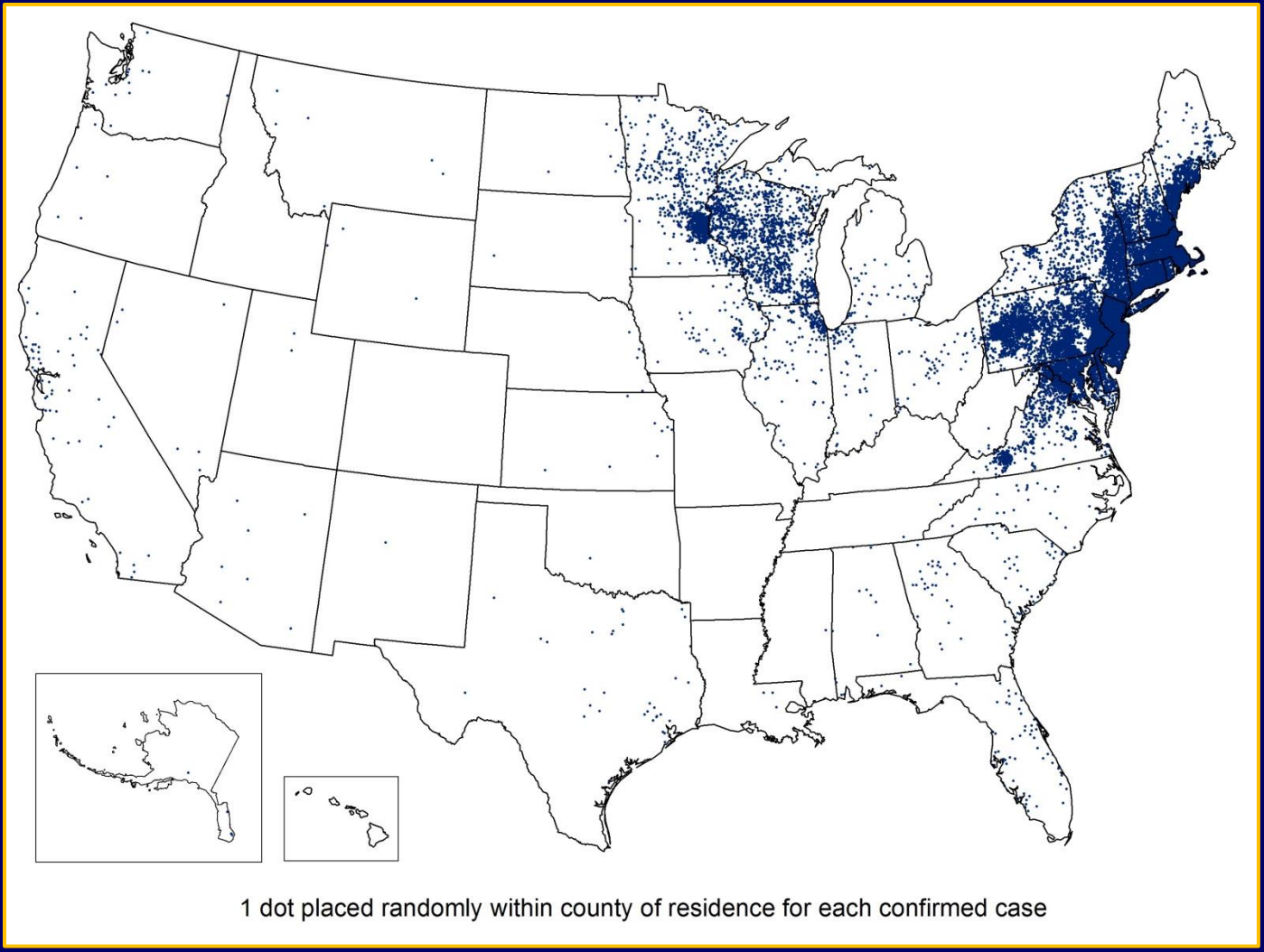
Life cycle of *Ixodes scapularis*



Confirmed Lyme Disease Cases by Month of Disease Onset--United States, 2001-2010



Reported Lyme Disease Cases, 2012



NOTE: Cases are reported based on patient's county of residence, which may be different from where they were infected.

Erythema Migrans (EM)

- 70-80% of cases
- ~7-14 days after tick bite
- Expands over days
- Rarely painful
- Distinguish from allergic reaction

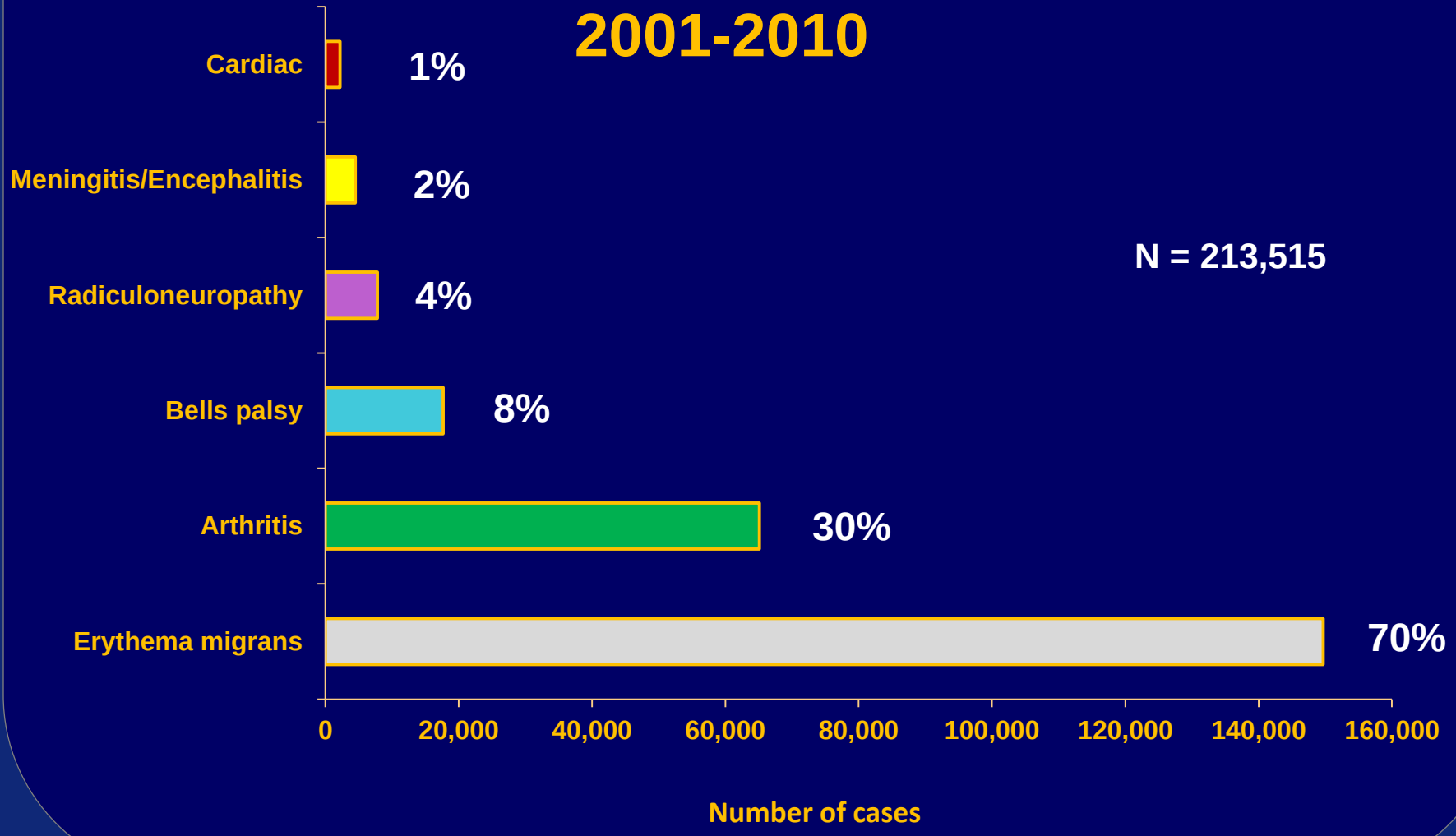
Atypical EM Presentations

Nadelman RB, Wormser GP. Management of tick bites and early Lyme disease. Rahn DW, Evans J eds. *Lyme disease*. 1998; Philadelphia: American College of Physicians. 49-75.

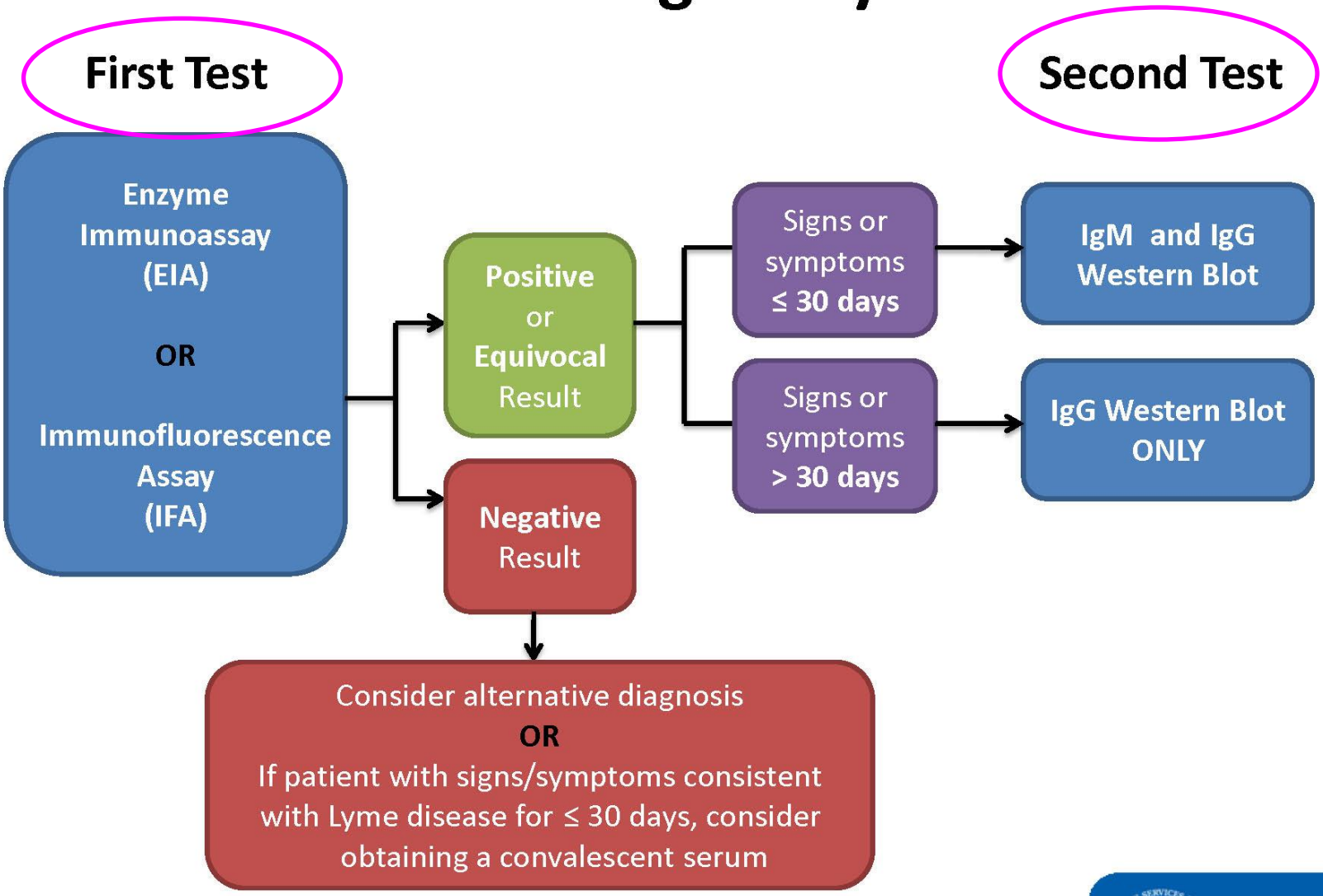
Disseminated and Late Lyme Disease

- Facial palsy
  - Summer months
  - May be bilateral
  - ± CSF pleocytosis
- Arthritis
  - Intermittent
  - Oligoarticular
- Late-stage neurologic
  - Peripheral neuropathy
  - Encephalopathy

Clinical Signs of Confirmed Lyme Disease Cases—United States, 2001-2010



Two-Tiered Testing for Lyme Disease

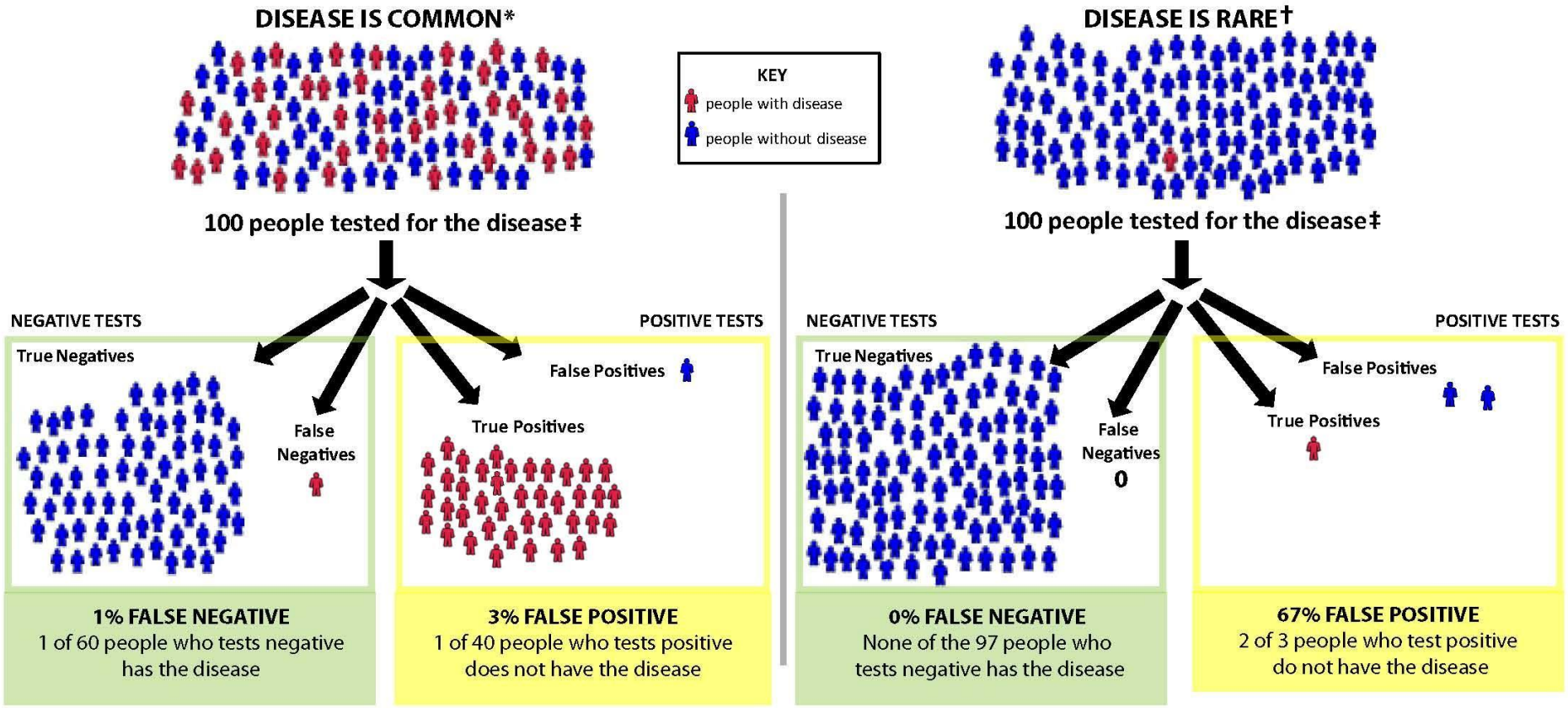


Understanding Test Results for Infectious Diseases

Consider the likelihood of disease ***before*** performing laboratory testing

The likelihood that a patient has a disease depends on many factors:

- **Has the patient been in an area where the disease is found?**
- **Does the patient have signs and symptoms typical of the disease?**
- **Does the patient have risk factors for contracting or developing the disease?**



* 40 out of 100 patients in this area have the disease.
† 1 out of 100 patients in this area have the disease.

‡ Test specificity = 98% (high) and test sensitivity = 98% (high)

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Division of Vector Borne Diseases | Bacterial Diseases Branch

Sensitivity of Two-Tiered Serologic Testing

Lyme Disease Stage	Sensitivity (%)*
EM rash (acute)	38
EM rash (convalescent)	67
Early neurologic	87
Late neurologic	100
Arthritis	97

*Specificity of two-tiered testing is generally ≥ 95%

Bottom line:

- Good in later stages of disease
- Testing of EM patients not generally necessary

Bacon et al. JID 2003; 187:1187–99

Additional Tests: Questionable Utility

- Single-tier IgM or IgG immunoblot tests without a previous EIA/IFA
- In-house criteria for interpretation of immunoblots
- Capture assays for antigens in urine
- Tests for “cystic forms” of *B. burgdorferi*
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays
- Measurements of antibodies in joint fluid (synovial fluid)
- Novel culture techniques

More info on www.cdc.gov/Lyme

Red Flags for Alternative Labs

- Tests offered are not FDA approved
- Laboratory claims to “specialize” in Lyme and other tick-borne disease testing
- Do not accept insurance → patient pays out of pocket ($500 - $1,000 ++)

Treatment – Adults

- **Tick bite prophylaxis –** doxycycline 200 mg po x1 (only in certain circumstances)
- **Erythema migrans:**

  Doxycycline 100 mg po bid x 14 days or

  Amoxicillin 500 mg po tid x 14 days or

  Cefuroxime 500 mg po bid x 14 days
- **Patients with multiple EMs, facial palsy, and/or arthritis can be treated with the same oral regimens**

  Duration 14-28 days, depending on clinical picture

From: The Clinical Assessment, Treatment and Prevention of Lyme disease, Human Granulocytic Anaplasmosis and Babesiosis: Clinical Practice Guidelines from the Infectious Diseases Society of America; CID; 2006

Treatment – Adults Continued

- Carditis can be treated with oral or IV antibiotics x 14 days.
- Nervous system disease is treated with IV antibiotics x 14 days.
- Patients with recurrent arthritis should be retreated with oral antibiotics (28 days) or IV antibiotics (14 days).
- NOTE: This is a summary of treatment options. See published guidelines for more details and special situations. Available at: IDSA website (www.idsociety.org).

The Clinical Assessment, Treatment and Prevention of Lyme disease, Human Granulocytic Anaplasmosis and Babesiosis: Clinical Practice Guidelines from the Infectious Diseases Society of America; CID; 2006

Prognosis

- Most patients treated with antibiotics recover completely
- In patients with persistent or recurrent joint swelling, re-treatment with a second 4-week course may be needed
- Some patients – particularly those diagnosed with later stages of disease – may have persistent symptoms of fatigue, muscle aches, reduced concentration
  - Preferred term for this is Post-Treatment Lyme Disease Syndrome (PTLDS)
  - Studies have not shown that long-term antibiotic treatment is beneficial

Death from Prolonged Antibiotic Therapy for Lyme Disease

- 30-year-old woman received 27 months IV ceftriaxone through catheter
- Death due to embolization of large *Candida* septic thrombus
- Record provided no clear evidence for diagnosis of Lyme disease

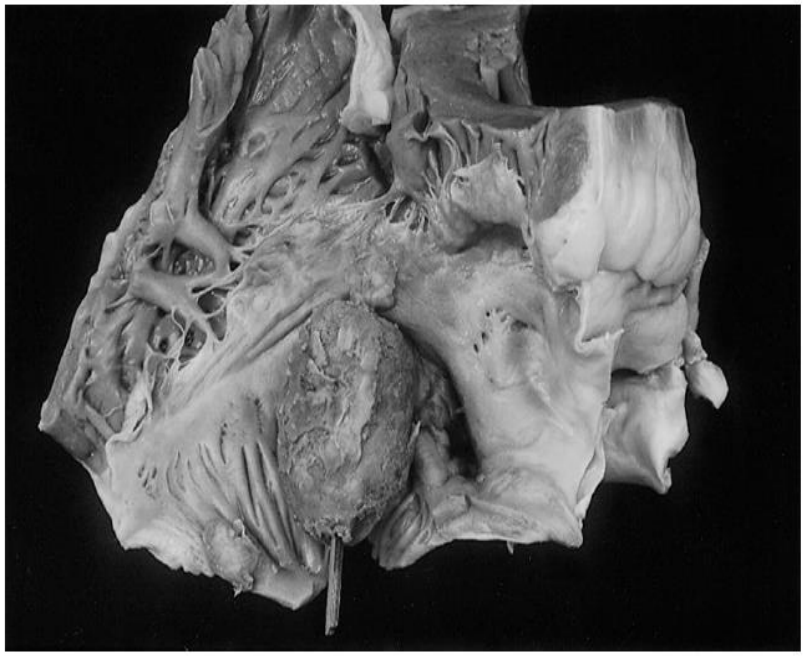


Figure 1. Opened right atrium from a patient who died because of inappropriate therapy for Lyme disease. The photo shows a large infected thrombus on the fractured tip of the patient's Groshong catheter.

Patel et al. CID 2000: 31:1107-9

STARI or Lyme Disease?

- Southern Tick-Associated Rash Illness (STARI)
  - Rash indistinguishable from Lyme disease EM
  - May be accompanied by fatigue, fever, headache, muscle and joint pains
  - Follows bite of lone star tick, *Amblyomma americanum*
- Also known as Master's disease
- Cause of STARI is not known

Southern Tick-associated Rash Illness (STARI)

Life stages of lone star tick (*Amblyomma americanum*)

Treatment of STARI

- It is not known whether antibiotic treatment is necessary or beneficial for patients with STARI
- STARI has not been linked to arthritis, neurologic disease, or chronic symptoms
- Nevertheless, because STARI resembles early Lyme disease, physicians will often treat patients with oral antibiotics
  - Lantos et al. model → observe is preferred strategy in places where Lyme disease is rare

Lantos et al. Empiric antibiotic treatment of EM-like skin lesions as a function of geography: a clinical and cost effectiveness modeling study. Vector Borne Zoonotic Dis 2013;13(12):877-83.

Prevention – Talk About It!

- Avoid tick habitat
- Use DEET (at least 20%) or wear permethrin-treated clothing
- Shower soon after being outdoors
  - Washes away unseen nymphs and gets tick infested clothing off of the body
- Daily tick checks—remove attached ticks ASAP
- Treat pets appropriately for ticks year-round
- Call your provider if you develop a fever or rash

Tick-borne rickettsial diseases

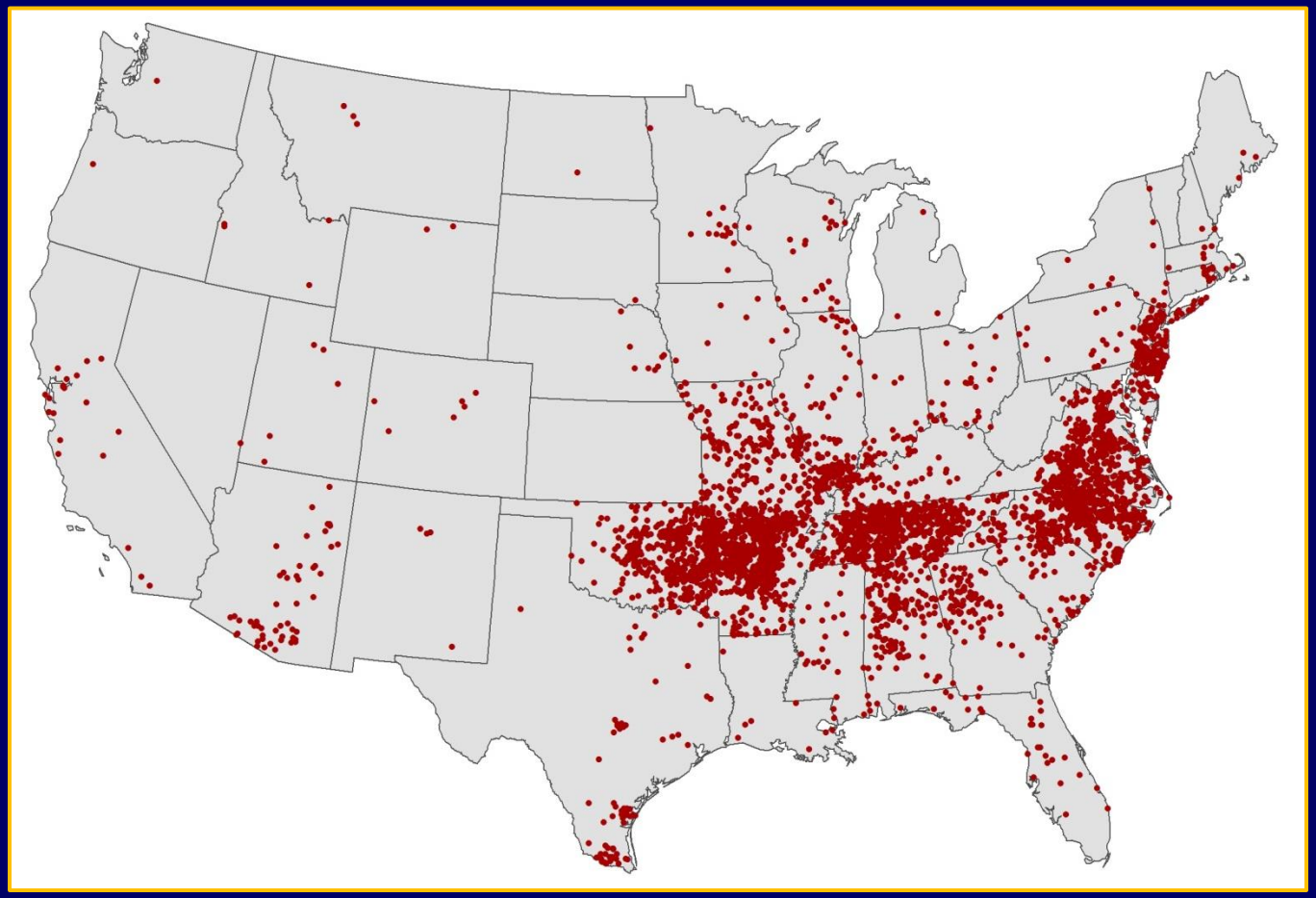
Including Rocky Mountain spotted fever (RMSF), Ehrlichiosis, and Anaplasmosis

- **Severe and potentially fatal**
- **Rapidly progressing**
- **Similar clinical presentation**

But…

- **Are all treated with doxycycline**
- **Use similar laboratory diagnostics**

Reported Cases of Rocky Mountain spotted fever, 2012



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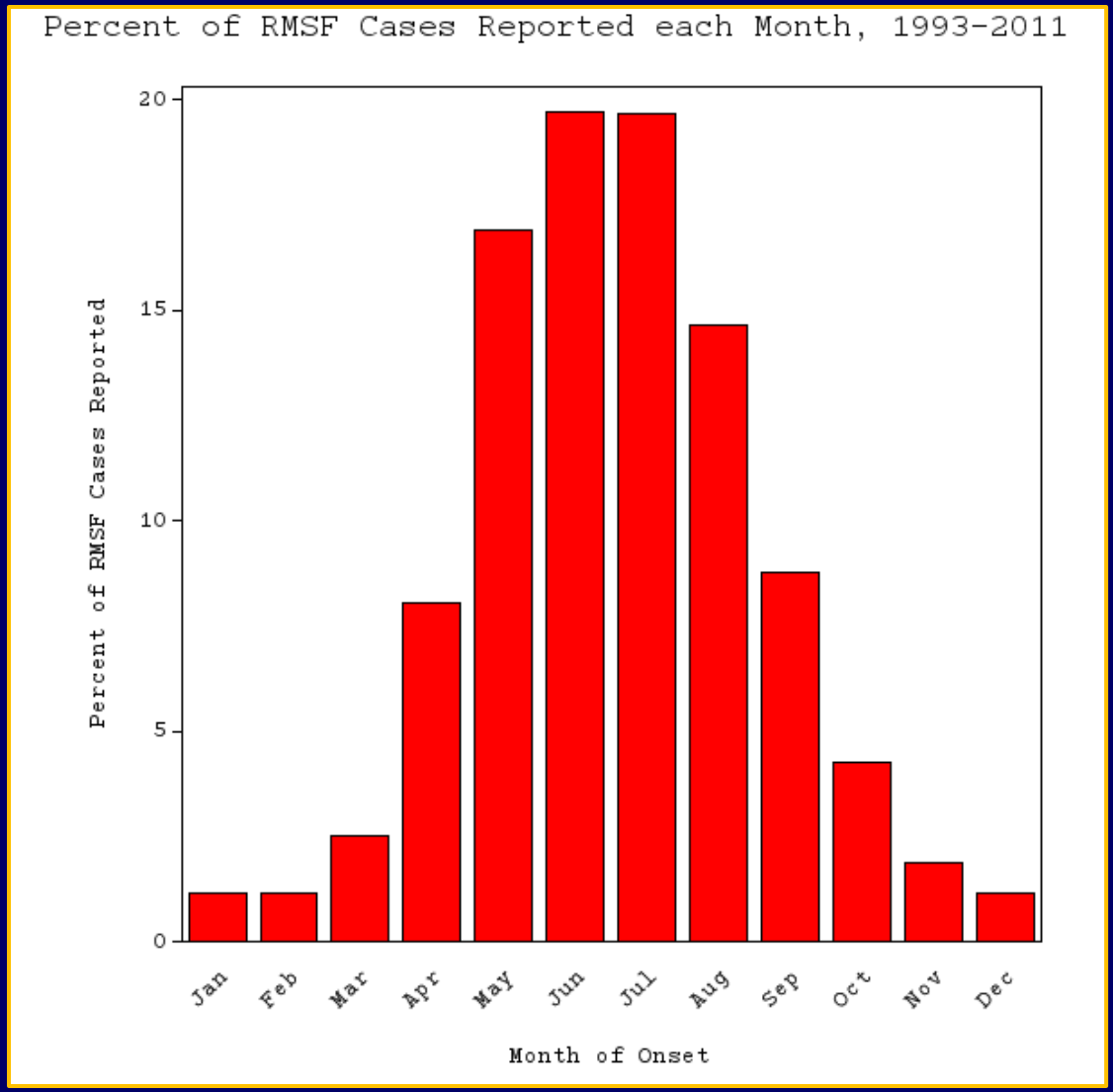
RMSF—Seasonal distribution



RMSF—Primary tick vectors

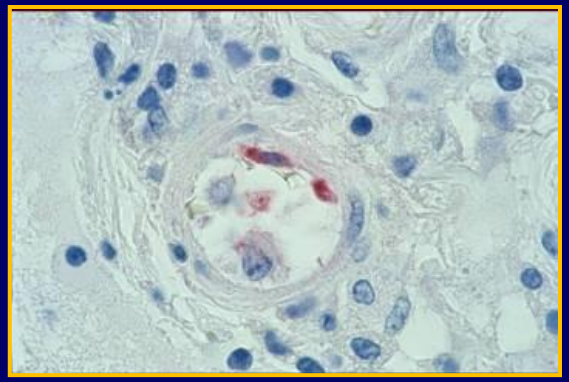
Dermacentor variabilis
American dog tick

Dermacentor andersoni
Rocky Mountain wood tick

Rhipicephalus sanguineus
Brown dog tick

Rocky Mountain spotted fever

- Tick-borne intracellular bacteria *Rickettsia rickettsii*
- Infects endothelial cells, causes vasculitis
  - Non-specific symptoms
  - multi-system organ failure
- No “classic” presentation
- Rapidly fatal
  - Median time to death 8 days
  - >20% case fatality rate in untreated cases



RMSF: early clinical manifestations (Day 1-4)

- **Day 1-2**: fever, headache, myalgia *(may be responsive to OTC pain/fever meds)*
- **Day 2-4**: May develop respiratory signs (cough, community-acquired pneumonia) and/or gastrointestinal signs (nausea, vomiting, abdominal pain)
- **Day 2-4**: light maculopapular rash *may* appear
- **Day 2-4**: Thrombocytopenia, hyponatremia, elevated liver enzymes (AST, ALT) *may* occur

RMSF: late clinical manifestations (Day 5 or later)

- Worsening systemic illness (cough, dyspnea, arrhythmias, hypotension, severe abdominal pain)
- Petechial rash may develop
- Thrombocytopenia, hyponatremia, elevated liver enzymes (AST, ALT) usually present
- Onset of neurologic signs (photophobia, altered mental status, seizures)

RMSF treatment

- **Treat early, based on clinical suspicion and exposure history**
  - Do not wait for lab results – may be negative early during the course of infection
  - Use exposure history as a guide- keep in mind tick bite only reported in 60% of cases
- **Doxycycline is the drug of choice for adults and children of all ages**
  - Improvement often seen in 24-72h
  - Other broad-spectrum antibiotics are not effective
  - Sulfas, fluoroquinolones may cause more severe disease

Doxycycline and RMSF in children

- Recent studies have shown that health care providers hesitate to use doxycycline in children under 8 years
- Not shown to cause dental staining at the recommended dose and duration, even multiple courses
- *OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED*
- CDC and the American Academy of Pediatrics (AAP) recommend doxycycline as first line treatment for RMSF in children

Doxycycline dose/duration for RMSF

Adult or child ≥45 kg

↓

Doxycycline
100 mg bid
p.o. or i.v.,
5-10 days

Child <45 kg

↓

Doxycycline
2.2 mg/kg/day
bid p.o. or i.v.
5 days (or 3
days past
defervescence)

Pregnant adult
or
Life-threatening
tetracycline allergy

↓

*Consult with infectious disease specialist

**In rare cases, chloramphenicol may be considered as an alternative, but patients have higher risk of fatal outcome*

Testing for RMSF

- Testing is used for surveillance and public health (magnitude of cases, confirm risks)
- No early diagnostic test can definitively rule RMSF in or out
- Do not base treatment decisions on (or wait for) test results

RMSF diagnostic tests

- PCR or IHC of whole blood, serum, tissue
  - Most accurate for severely ill/fatal cases
  - Unlikely to be positive for mild RMSF or samples taken early (day 1-4 of illness)
- Serology (IFA)
  - Detects antibodies
  - Testing of paired sera (acute, convalescent 2-4 weeks later) recommended
  - Can be difficult to interpret
    - Often negative during acute illness
    - Antibodies from prior infections may persist for years

New developments in RMSF

- Brown dog tick has been implicated as a vector for RMSF on American Indian Reservations in the Southwestern United States and Mexico
- More peridomestic and domestic exposures associated with the brown dog tick
- Associated with high case fatality rate and unusually high incidence
- Children are especially vulnerable to infection

Ehrlichiosis and Anaplasmosis—epidemiology, diagnosis, and treatment

Female lone star tick—transmits *Ehrlichia chaffeensis*

Female blacklegged tick—transmits *Anaplasma phagocytophilum*

Ehrlichia chaffeensis—2012

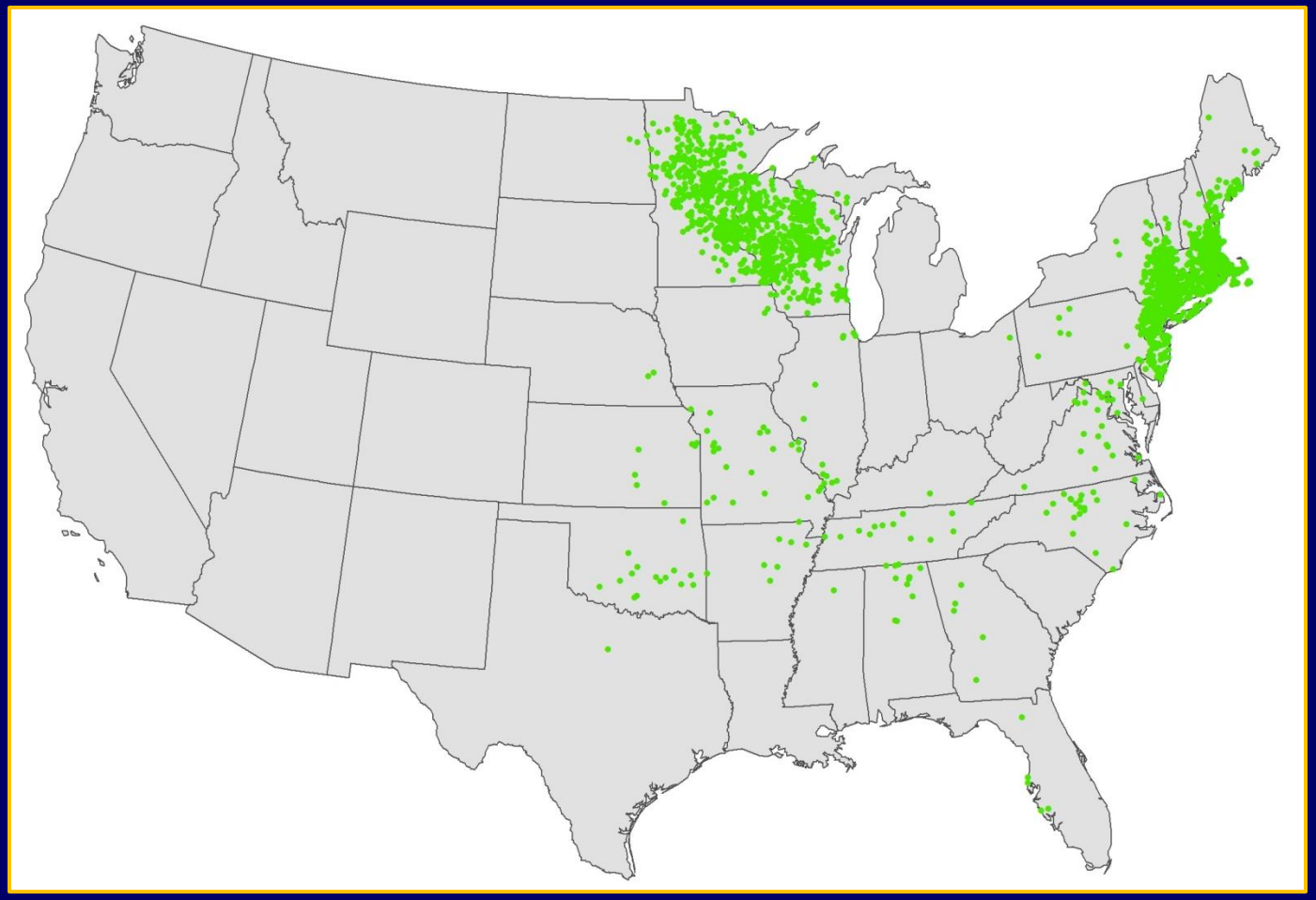
One dot placed randomly within county of residence for each confirmed case. Cases are reported from the infected person's county of residence, not necessarily the place where they were infected.

Symptoms—Ehrlichiosis

- Fever / chills
- Headache / malaise
- Muscle pain
- Nausea / vomiting / diarrhea
- Confusion
- Rash
  - In up to 60% of children, less than 30% of adults
  - Macular, maculopapular (early) or petechial (late)
- Thrombocytopenia, leukopenia and elevated liver enzymes

Severe clinical presentation may include multiple organ failure, septic shock, or respiratory failure.

Anaplasma phagocytophilum—2011



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Symptoms—Anaplasmosis

- Fever / chills
- Headache/ malaise
- Muscle pain
- Nausea / abdominal pain
- Cough
- Confusion
- Rash (rare with anaplasmosis)
- Thrombocytopenia, leukopenia and elevated liver enzymes

Severe clinical presentations may include respiratory failure, renal failure or toxic-shock-like syndrome.

Note on blood transfusions and organ transplants

- Both ehlichia and anaplasma species infect the leukocytes
- Transfusion-associated and solid-organ transplant transmissions have been reported in the US
- Donors may be asymptomatic
- Leukoreduced blood products may reduce the risk of transmission, but does not eliminate it altogether
- Patients who develop either disease within a month of blood or organ donation should be reported to state health departments

Treatment—Ehrlichiosis and Anaplasmosis

- Treat as soon as the disease is suspected
- Adult – Doxycycline 100mg BID until 3 days after fever resolves
- Pediatric – Doxycycline 2.2 mg/kg BID until 3 days after fever resolves
- This treatment regimen has not been proven to cause dental staining, even with repeated use
- If anaplasmosis is suspected, patients should be treated with doxycycline for 10-14 days to provide appropriate length of therapy for possible incubating co-infection with Lyme disease

Testing for Ehrlichiosis and Anaplasmosis

- Testing is used for surveillance and public health (magnitude of cases, confirm risks)
- No early diagnostic test can definitively rule ehrlichia/anaplasma in or out
- Do not base treatment decisions on (or wait for) test results

PCR—Ehrlichiosis and Anaplasmosis

- During acute illness test using PCR on whole blood.
  - Most sensitive in the first week of illness, and quickly decreases in sensitivity following the administration of appropriate antibiotics
  - PCR is currently the only diagnostic test able to adequately distinguish between ehrlichia and anaplasma species
  - PCR far more sensitive for Ehrlichiosis and Anaplasmosis
  - Even so, a negative result does not completely rule out the diagnosis

Serology—Ehrlichiosis and Anaplasmosis

- The gold standard serologic test is the indirect immunofluorescence assay (IFA) using species-specific antigen, performed on acute and convalescent sera
  - The first sample should be taken in the first week of symptoms
  - The second sample should be taken 2 to 4 weeks later.
  - Positive samples should demonstrate a significant (four-fold) rise in antibody titers
  - IgM antibodies are less specific than IgG antibodies and more likely to result in a false positive

For more information…

- **MMWR March 31, 2006/Vol. 55/No. RR-4**
  - **Updates coming soon!**

Thank you!

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

To Ask a Question

- **Using the Webinar System**
  - “Click” the Q&A tab at the top left of the webinar tool bar
  - “Click” in the white space
  - “Type” your question
  - “Click” ask

- **On the Phone**
  - Press Star (*) 1 to enter in the queue to ask a question
  - State your name
  - Listen for the operator to call your name
  - State your organization and then ask your question

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